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August 30, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: DOCKET NO. OON-1380

Dear Staff:

Enclosed are two copies of our Final Comments for the "Proposed Approach to Regulation of Cellular and Tissue-based Products" by the FDA.

Dr. Periera requested that we send two copies to your attention for review. We also forwarded two copies to Kathy Eberhart (CBER, HFM-49).

At the end of our comments, we requested a meeting to review the enclosed comments and the proposals from Telos on the new Proposed Approach from the FDA. This would allow us to answer or address all points and formal proposals presented in our final comments.

Thank you and we look forward to hearing from you.

Sincerely,

Al Austin
Telos Medical LP

OON-1380

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Docket No. 00N-1380
Written Comments
to
FDA Public Meeting August 2 2000: Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopaedic Reconstruction and Repair

by
Telos Limited Partnership
Fallston, MD
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Telos, as an interested party in the development of FDA's "Proposed Approach to Regulation of Cellular and Tissue-Based Products" (Proposed Approach), presented its views during the above meeting. The topics attempted to address five questions put to the public by the FDA. We would like to add, and/or reinforce our position with, the following comments and observations pursuant to this meeting.

1) Which processing procedures applied to human bone allografts fall within, or outside of, FDA's proposed definition for "minimal manipulation"?

In the Proposed Approach examples are given of widely used minimal manipulation processes such as gamma irradiation and ethylene oxide sterilization and lyophilization. However, gamma irradiation of bone allografts at exposure levels required to effectively destroy the HIV bioburden or reach a sterility assurance level (SAL) of 10^{-6} can severely affect the biomechanical characteristics and osteo-integration performance of these allografts; this process then is unable to meet the definition as a "minimal" manipulation process. Additionally, these three processing examples cited can have a significant adverse effect on bone allograft performance and biomechanical characteristics at high levels of exposure or if used in combination with each other (references available upon request).

Telos is a proponent of the use of moderate moist heat treatment (<100°C) which has been used over the last 8 years throughout Europe, as well as in Japan, and recently in Canada. This processing technique for femoral heads from living surgical donors has been routinely used in the hospitals to decontaminate more than 60,000 of these allografts. The reduction factor for this robust decontamination process is >8.3 (log_{10}) for HIV and >9.06 (log_{10}) for CPV. Each allograft processed with this technique is treated in a uniform and consistent manner, regardless of allograft size. Moderate moist heat treatment does not alter the original relevant characteristics of the allograft relating to the tissue's utility for reconstruction, repair, or replacement. Clinical osteo-integration rates are similar to other minimal manipulation micro-organism inactivation techniques such as gamma irradiation (at low exposure levels). The total costs of a femoral head processed in this way is about $290 per head while a femoral head from a bone bank in the USA typically costs $1,000-$1,300 per head (processed or unprocessed). Cancellous bone taken from these femoral heads is the most used bone allografts in the United States and many credible and knowledgeable individuals have trouble justifying the exorbitantly high prices of these grafts which are donated to tissue banks free of charge and processed, stored and administered by tissue banks which are supposed to be non-profit organizations.

While moderate moist heat treatment of homologous structural bone allografts from surgical donors is not currently performed in the USA, the FDA is requested to explicitly include moderate moist heat treatment as an example of minimal manipulation in any final documents regarding the Proposed Approach because it can 1) significantly lower the costs of cancellous bone allografts to the U.S. public health care system, 2) add greater allograft viral and bacterial inactivation safety, 3) process each allograft in a uniform and consistent manner, and 4) maintain the allograft's biomechanical characteristics and clinical performance.

Additionally, CDC published a study in 1994 where they concluded "antibody assays licensed by the FDA... may be unable to detect divergent HIV strains". In order to avoid false over-reliance on serological testing we believe that minimal manipulation processing for viral and bacterial inactivation should be required of all allograft cancellous bone and not just be optional.

2) Which uses of human bone allograft fall within, or outside of, FDA's proposed definition for "homologous use"?

In 1999 in the USA about 650,000 allogenic bone transplantations were performed. 80-90 % of these transplantations involve the use of cancellous bone sourced from excised femoral heads of patients (living surgical donors, not brain-dead) undergoing total hip arthroplasty. This allograft bone is typically cut or gound into chips, blocks or particulate and used as a bone void filler to fill bone defects or to place in a joint undergoing fusion. We believe these uses, taking cancellous bone from one location and transplanting this allograft to a different location but where cancellous bone growth is now desired, should fall under the definition for "homologous use".

3) What risks to health have been identified and characterized for human bone allograft products?

The disease (HIV, hepatitis B and C) transmission risk appears to be very low for bone allografts. However, reporting procedures appear to be uncentralized and only marginally existent on either a national or even state level. The Centers for Disease Control and Prevention has informed us that up until about two years ago, only certain states required incidents or suspected incidents of disease transmission or infections resulting from organ or tissue transplants to be reported by law. CDC has only semi-organized information on HIV transmission from organ or tissue transplantation and apparently no organized data on the numbers of hepatitis B and C transmissions due to organ and tissue transplantations. It is too easy (and potentially dangerous) to conclude that the viral transmission risks are nonexistent or very low when there is no finalized, coordinated approach with mandatory reporting requirements to make a real assessment.

In its Proposed Approach FDA makes no distinction between allograft bone harvested from cadavers versus allograft bones harvested from living surgical (not brain-dead) donors, even though these two allograft sources have significantly different risk profiles. Especially with regard to surgical femoral head allografts, the donor (hip patient) is available for an extensive screening (ie. patient medical history and interview) procedure and post-donation followup. It is fairly common knowledge that a complete and extensive screening procedure is the single most important

factor in reducing risk of virus transmission with tissue allografts. Furthermore, these older donors tend to come from a low risk group for transmissible viruses. However, the AATB Standards for Tissue Banking (1998) require living donors of surgical bone allografts to be retested at 6 months for HIV and hepatitis infections whereas this requirement does not exist for cadaver donors of bone allografts. The result of these requirements is that surgical bone allografts are held to a higher (and in the FDA's Proposed Approach to the same) safety standard compared to cadaver bone allografts while the risk of viral transmission is lower for surgical bone allografts.

Furthermore, bone allografts from cadavers are typically shipped to or come from all parts of the United States or even outside the United States whereas allografts from surgical donors, processed with moderate moist heat treatment, remain local. Both surgical bone donor and recipient are patients of the same surgeon offering a closed loop between donor-recipient-surgeon. Additionally the surgical allograft bone never has to leave the hospital, not even for processing, if using moderate moist heat treatment. There is better traceability and trackability of graft, donor, and recipient when using surgical allografts from living donors. The surgical bone donor has the added emotional satisfaction of helping someone in their community, assured that their bone will not end up in some other part of the world, and the recipient is gratified that the donor is local, known to the surgeon, and well screened as opposed to receiving bone from distant origins.

4) What controls have been identified to adequately address the risk to health of human bone allograft products?

In its Proposed Approach FDA should make a distinction between surgical (living) donors and cadaver donors of allograft bone. Currently, surgical donors, of whom the hospital and/or surgeon have a complete medical history and are often low risk patients in terms of disease transmission, are held to a higher standard by AATB or the same standard by FDA compared to cadaver donors, on whom the hospital and/or doctor will, most likely, possess less information. The cadaver donor is also not available for post-donation testing or evaluation. In keeping with FDA's approach that higher risk bone allografts should be held to higher safety standards, FDA should require in any finalized regulations that all cadaver sourced bone allografts:

a. be harvested only from multi-organ donors
b. be held in quarantine until mandatory 6 month post-implantation HIV and hepatitis (B and C) blood tests are performed on the recipient of a vital organ (heart, liver, kidney) from the same donor.

In this way the 6 month window period for seroconversion of these viruses can be respected in these higher risk bone allograft donors.

For surgical living (not brain-dead) donors we believe FDA's approach should be to not require 6 month repeat serological testing if a robust viral and bacterial inactivation minimal manipulation treatment on these allografts is performed to remove the risk of undetected viral infections for those viruses which are tested as well as not tested.

5) What industry standards for bone allograft products are available, and what standards will be needed in the future?

Gamma irradiation treatment or sterilization is the preferred micro-organism inactivation technique and is currently used by half the tissue banks in the USA. Yet the principles of this technology are not widely understood. All too often the ritual dose of 25 kGy (or lower: AATB 1998 Standards call for only 15 kGy minimum) is given in the confident belief that it is a sufficient and safe dose to use routinely without employing allograft-specific process validation studies. Recent publications suggest that the dose required to inactivate the HIV bioburden in homologous structural bone allografts is 35 kGy and the doses required to achieve a SAL of 10^{-6} can range from 36 up to 89 kGy. At these levels the biomechanical characteristics and osteo-integration performance of these allografts is significantly adversely affected. One researcher concluded, therefore, that "gamma irradiation should be disregarded as a significant virus inactivation method for bone allografts". We feel that allograft-specific viral and bacterial inactivation studies should be performed (ie. kinetics of virus decay should be investigated and reduction factors generated based on the size or density of the allograft at the worse case viremia), and standards issued, to validate the effectiveness of the viral inactivation minimal manipulation processes used by the cancellous bone allograft supplier.

Additionally, there should be, at minimum, a biomechanical and architectural characterization of the bone allografts processed by a viral and bacterial inactivation validated minimal manipulation process to insure that the process does not significantly adversely affect the relevant characteristics of the allograft through the range of sizes and bone densities intended to be processed. Many of the processing techniques used today on bone allografts can and do have detrimental effects on bone allografts.

We kindly request a meeting with the relevant FDA personnel to discuss the above points in more detail prior to the Proposed Approach being finalized.